THE EFFECTS OF TRANQUILLIZATION: Benzodiazepine Use In Canada

R. Cooperstock
Scientist
Addiction Research Foundation

J. Hill
Regional Director Ontario
Health Promotion Directorate

Cover photograph was provided by R. Cooperstock

Published by authority of
The Minister of National Health and Welfare
1982.

Également disponible en français sous le titre
LES EFFETS DE L'USAGE DE TRANQUILLISANTS:
l'usage des benzodiazépines au Canada.

TABLE OF CONTENTS

	ACKNOWLEDGMENTS	4
1.	INTRODUCTION	5
2.	OVERVIEW OF BENZODIAZEPINE USE	6
	General Canadian Data	6
	High Risk Groups:	10
	Women	10
	The Elderly	13
	The Chronically Ill	15
	The Institutionalized	17
3.	APPROPRIATE USES OF BENZODIAZEPINES	19
	Use as Anti-Anxiety Agents and Hypnotics	19
	Use in Non-Psychiatric Conditions	19
	Psychiatric Contraindications	20
	Duration of Use and Dosage	20
	Appropriateness in Pregnancy, Pediatric Medicine, the Elderly	21
4.	UNDESIRABLE PHYSIOLOGICAL AND PSYCHOSOCIAL CONSEQUENCES OF USE	23
	Physical Effects:	23
	Dependence and Withdrawal	24
	Motor and Cognitive Impairment	25
	Benzodiazepines as Hypnotics	26
	Polydrug Use and Cross-Addiction	27
	Overdose and Poisoning	30
5.	FACTORS AFFECTING PRESCRIBING AND CONSUMPTION	32
	Biomedical Model of Illness	33
	Physician-Patient Relationships	34
	Organization of Medical Care	37
	Drug Promotion and Advertising	41

6. SOCIAL MEANING OF BENZODIAZEPINE USE 45
7. SUMMARY AND CONCLUSION 49
8. APPENDIX A: BENZODIAZEPINES SOLD IN CANADA, 1981 52
9. APPENDIX B: GLOSSARY OF MEDICAL AND DRUG-RELATED TERMS 54
10. REFERENCES 58

ACKNOWLEDGMENTS

The authors wish to thank Professor E. Vayda, Associate Dean, Division of Community Health, Faculty of Medicine, University of Toronto, who contributed extensively to an earlier version of this document and has provided a continuing supply of information and support. Dr. Usanda Busto, Research Fellow, Clinical Pharmacology Program, Addiction Research Foundation, gave freely of her time and expertise. Dr. H.L. Lennard was an active participant in preliminary discussions which resulted in this paper. Particular thanks go to Jennifer Evans for her editorial and typing skills and her intelligent role as 'every-woman'. We also wish to thank our seven reviewers for their thorough and constructive comments.

INTRODUCTION

During the past two decades, there has been a proliferation of psychotropic* chemical agents developed by the pharmaceutical industry, prescribed by physicians and used by consumers. Among the most widely used psychotropic drugs are the benzodiazepines. One of the most popular drugs in this class in Canada for many years has been diazepam (most common trade name, Valium). This is only one of 10 benzodiazepines marketed in Canada and while they are advertised for a variety of purposes they all share common sedating properties.

Concern with benzodiazepine use in Canada has been expressed by consumers of health services, professionals and government agencies. The purpose of this document is to bring together information on these drugs, including extent of use, appropriate indications, contraindications, and some of the problems associated with their use. These include dependence, polydrug use, overdose, and the risk to some segments of the population who receive large quantities of these drugs.

In addition, factors impinging on drug use such as the structure of the health care system, its philosophical view of illness, and physician-patient relationships are discussed. Finally, some of the social consequences and meanings of extensive benzodiazepine use are explored.

Health and Welfare Canada has chosen to publish this document as an indication of their concern with the issues posed, and in order to provide an informed basis for further discussion by those responsible for the provision of health services to the Canadian population.

*For a glossary of the medical and drug-related terms used in this document the reader is referred to Appendix B.

OVERVIEW OF BENZODIAZEPINE USE

General Canadian Data

As of 1981 there were 10 different benzodiazepine drugs sold in Canada.* This class of drug was first introduced as an anti-anxiety agent (chlordiazepoxide), then was recognized as also containing muscle relaxant properties (diazepam), then was marketed as an hypnotic (flurazepam), and most recently as an anticonvulsant (clonazepam). The benzodiazepines were introduced into Canada in 1960 with chlordiazepoxide (most popular trade name Librium), followed two years later by diazepam, most commonly prescribed as Valium. This latter drug quickly became the most popularly prescribed drug in the Western world.

Of some difficulty for both prescriber and consumer is the fact that some benzodiazepines are sold under a variety of trade and generic names. Diazepam, for example, is sold as 15 trade name products, including Valium, and four generics. Similarly, chlordiazepoxide can be purchased under 13 separate trade names and is also supplied by six companies under its generic name. Finally, oxazepam, most popularly sold as Serax, is distributed under three competing trade names and one generic.

Although the benzodiazepines are marketed as having a variety of functions, including anti-anxiety, hypnotic, and anticonvulsant, they "are all similar structurally and in their pharmacological actions. Few have specific advantages over others."[1] One factor which does differentiate these substances is the half-life of each drug. Half-life refers to the time required for the drug concentration in the plasma to decrease by one-half. The most popular benzodiazepine, diazepam, used as both a sedative and hypnotic, has a particularly long half-life. That is, it can be found in the

*Appendix A of this report gives the generic names of all 10 benzodiazepine drugs, their dates of introduction to Canada, the names of the manufacturers distributing in Canada, and the trade names under which the drugs are sold.

plasma for a mean period of 30 hours, ranging from 20 to 170 hours. Flurazepam, the most commonly used hypnotic, has an active metabolite whose half-life has a range from 47 to 100 hours. In contrast, oxazepam has a short half-life, approximately four to seven hours, and has no active metabolite.[2] These variations in the half-life and in the pharmacological action of the metabolites of the drugs appear to be of significance for prescribing, especially for those who metabolize drugs slowly, such as the elderly or individuals with liver disease.

Another group of benzodiazepine drugs are 'mixed' or combination drugs which contain a benzodiazepine in addition to one or more other active ingredients. The most popular of these in Canada is Librax, a combination of chlordiazepoxide and an anticholinergic which is used in treating gastrointestinal disorders and peptic ulcer. Mixed drugs are more frequently identified by their more specific action rather than as anti-anxiety agents, with the consequence that many individuals are unaware they are consuming a benzodiazepine. From an epidemiological viewpoint, combinations are not generally identified as such in surveys or prescription studies.

Two methods are commonly used to assess prescribed drug use. The first utilizes sales data or prescriptions dispensed through pharmacies or other outlets. This method focusses on drug distribution in contrast to the survey method, which measures consumption. Major methodological problems exist with both methods. Studies of prescriptions generally collect data from retail pharmacies, thus omitting other institutions, such as hospitals, nursing homes, prisons. (Hospitals alone account for approximately eight per cent of all drugs dispensed). By counting prescriptions for a product one can only know that the prescription was filled, but can never identify whether the substance was consumed at all, by whom, and in what quantity.

In contrast to sales data, surveys ask directly about consumption. Typically, they are conducted using a random or other type of community sample and thus also omit the hospitalized or institutionalized. Surveys are, of course, limited by the questions they ask. Benzodiazepine use may go unrecorded unless specific drug names are requested under the broader headings such as 'tranquillizers' and 'sleeping pills'. Underreporting of consumption by high users, by those using a number of different drugs, and by those who feel some stigma attached to use, is common. Memory loss also accounts for underreporting if questions ask about consumption for more than a short time period.[3]

Neither of these methods is able to collect valid information on illicit use of benzodiazepines. Police records of pharmacy thefts would be necessary and assessment of street drug use requires other research methods. In summary, no one method of estimating consumption gives completely accurate data; combining data collected through both prescription studies and surveys provides the closest estimates of real use.

Cross-Canada data on benzodiazepine consumption is at best somewhat sketchy but is nonetheless reasonably consistent. Using surveys as a base, 13 per cent of Metro Toronto residents claimed to have used tranquillizers during 1971,[4] 14 per cent of Ontario residents claimed the same during 1976[5], and in a national survey conducted in 1977, almost six per cent of respondents said they had taken a tranquillizer during the previous 14 days.*[6]

While evidence exists that U.S. consumption is somewhat higher than Canadian for these drugs, it is of interest that 15 per cent of the American population said they had used diazepam during 1979 and four per cent had used flurazepam during the same period.[7]

*Not all studies of consumption distinguish clearly between major and minor tranquillizer use. Many unfortunately inquire only of 'tranquillizers', thus limiting accurate estimation of minor tranquillizer use. When citing research, the terminology used will of necessity be that of the research reports.

The Saskatchewan Prescription Drug Plan is the most comprehensive in Canada, covering virtually all residents and charging a set fee of $2.60 per prescription. All prescriptions are computerized, thus data on prescribed drug use are available for a total population. While it cannot be expected that prescribing will be identical across the country, these data are perhaps closest to generalizable of any collected in Canada. Fo, the last year reported (1977), it was found that 20 per cent of the provincial population received a prescription for a mood-altering drug; about half, or almost 10 per cent of the population, were prescribed minor tranquillizers.[8a] In a preliminary analysis of prescription data from 1977 through 1979 in Saskatchewan, a slight decline was found in the prescribing of minor tranquillizers. Simultaneously, however, other benzodiazepine sedative-hypnotics increased in use, suggesting little change in total benzodiazepine distribution over the three-year period.[8b]

The Ontario Ministry of Health conducts a yearly sampling of prescriptions dispensed throughout the province. These figures are comparable to those from Saskatchewan, showing that close to half of all psychotropic drugs are accounted for by minor tranquillizers and that there has been a steady increase in the use of non-barbiturate hypnotics such as flurazepam.[9] This can be partially accounted for by the decline in the prescribing of the barbiturates as hypnotics.

Consistent throughout all of the above studies, whether Canadian, American or British, is variation among subgroups of the populations studied. That is, women almost invariably receive twice as many prescriptions for benzodiazepines as men and the elderly receive significantly more than younger populations. These variations will be demonstrated and discussed in the following section.

While the total number of prescriptions is valuable baseline information, of considerably greater importance is the identification of those segments of the population who use these drugs over extended periods. In a summary of a number of U.S. studies, it was found (depending on the

method used) that anywhere from 33 to 85 per cent had used their drug for longer than two consecutive months.[10] A national survey of prescribed drug use in Britain conducted in 1977 reports that more than half of all psychotropic drugs had first been prescribed more than one year previously and almost half at least two years before.[11]

Repeat prescribing of these drugs appears to be common in Canada, as elsewhere. Bearing in mind that a prescription is typically written to last one month, the Saskatchewan study found that of those receiving prescriptions for mood-modifying drugs, 20 per cent received more than five prescriptions of the same drug type during one year.[12]

High Risk Groups*

Given the proportion of the population who have used or are currently using benzodiazepines, it is almost inevitable that some segment of that population will have problems as a consequence of use. Those segments of the population who use the highest proportion of these drugs, i.e. those at highest risk, require particular study, both to document the extent of their use and to assess the effects of the drugs in these populations.

The major high risk populations in Canada, as elsewhere, are women, the elderly and the chronically ill. In view of the longer life expectancy of women, and the fact that chronic illness is more common among the elderly, it is hardly surprising that elderly women as a group are the highest consumers of minor tranquillizers.

1. Women

It has been consistently demonstrated that adult females at each age level receive more prescriptions for psychotropic drugs than males.[13-16] The studies show between 67 and 72 per cent of these drugs are prescribed to females.

* "High risk" is used here and throughout the paper to refer to those with the greatest statistical probability of being prescribed benzodiazepines.

Other studies demonstrate that not only are women in receipt of the most prescriptions for minor tranquillizers at any one point in time, they are also at highest risk for receiving more prescriptions per year than men, and for continuing on these drugs over more years.[17-19] For example, an analysis of data from an Ontario prescription insurance agency for a three-year period 1970 to 1973, both confirmed the existence of the typical two to one ratio of female to male prescriptions for each of the time periods, and found that women who received a psychotropic prescription in 1970 had an almost 50 per cent chance of receiving a similar prescription three years later. This was less true for the males. The same study found twice the number of females as males receiving 10 or more prescriptions in a year, indicating steady use.[20]

The excess prescribing to women over men might appear to be solely a function of the higher number of physician visits by women. However, in an examination of physician visits in Ontario it was shown that the difference between the sexes in number of visits does not account for all of the excess prescribing to women.[21]

One variable, that of work status, remains consistent in its relationship with psychotropic drug use among both sexes.[22] Those who are retired, unemployed, or not in the labour force, are the highest consumers of psychotropic drugs.[23,24]

These findings need careful examination since they could be due largely to age. One study, however, found that at each age level, women who worked outside their homes reported lower psychotropic drug use than those who did not.[25] A significant correlation existed in this study between the amount of time spent working outside the home and drug use: 11 per cent of those in full-time jobs, 19 per cent of those with part-time jobs, and 25 per cent of those at home full-time, reported use in the previous two weeks. The same study asked about social activities outside the home such as club participation, sports and visits to friends. Relating this

'activity level' to psychotropic drug use, it was found that as activity decreases psychotropic drug use increases.

A possible explanation for the relationship between work status, activity level and drug use is general health. Holding age constant, it was found that use of psychotropics increased as the women's subjective health rating became more negative.[26] Another study also found higher use among those reporting a poorer health rating.[27]

The question remains then whether poor health or sex should be considered the critical causal factor in psychotropic prescribing. Three studies suggest that sex may well be the overriding variable. The first examined male-female differences in drug use among those admitted to medical and surgical wards in a large U.S. medical centre, and found 25 per cent of the women and 15 per cent of the men entering the hospital with prescriptions for psychotropics.[28] The second study found that prior to hospital admission to a Canadian psychiatric ward females had received more prescriptions than males for minor tranquillizers.[29]

An Ontario study also found that men and women with identical symptoms attending a family practice clinic received different numbers of minor tranquillizer prescriptions. The women received significantly more prescriptions than the men although there were few differences between them in the rate at which they received other therapies.[30]

Two hypotheses were tested in a study of a community mental health facility: 1) that women would be more likely than men to recognize the existence of their problems, and 2) that before seeking psychiatric help, women would be more likely to look to members of their intimate networks. This study concluded that women accept the self-label of psychiatric illness more willingly than men, and that having spoken to more intimates about their problem they enter treatment and accept the role of patient more readily than men, who are more typically pressured into treatment.[31]

Numerous studies have demonstrated a difference in men's and women's reporting of both physical and

psychological symptoms. It has been shown that men have less awareness of both emotional disorders,[32] and physical symptoms.[33] These variations in levels of awareness may well be related to differences in roles filled by men and women.

For example, women are expected to be nurturing, which involves responsibility for the health care of family members.* It also requires more contact with professionals through attendance at health care facilities with children and elderly parents, thus establishing comfortable and familiar relationships with health care staff.

Over 90 per cent of Canadian family practitioners are males, most of whom can be expected to hold traditional views of appropriate male and female behaviour. This would include greater expectation of and ease with expressive behaviour from females than from males. Having seen women patients frequently in a family context, doctors are again more likely to elicit information about family problems, emotional and social concerns. These may well be factors in the higher prescribing of benzodiazepines to women.

2. The Elderly

Widespread use of psychotropic drugs by the elderly poses a number of potential health hazards as the elderly have a diminished capacity to metabolize and eliminate drugs. Although the benzodiazepines are considered preferable to the barbiturates or other sedative-hypnotics, they are nonetheless problematic for the elderly. Since this population is most at risk for chronic illness and consequently for using a number of drugs concurrently, the risk of adverse drug reactions is higher among them. It has been shown that in a hospitalized population, adverse drug reactions occurred in three per cent of patients aged 20 to 29 but in 21 per cent of patients between 70 and 79.[34]

*This requires women to be considerably more sensitive than men to the physical and emotional health status of others.

The elderly receive more than twice the number of prescriptions for psychotropic drugs as do younger people.[35] As the ratio of the elderly in the population increases so can we expect increases in prescription and use of psychotropic drugs. All Canadian provinces now provide low cost or free prepayment prescription drug plans to those 65 and over. The Ontario Drug Benefit Plan covers approximately 1.2 million residents of the province, 800 000 of whom are age 65 and over. The average number of prescriptions for all drugs per eligible beneficiary has increased steadily since the introduction of the plan to the point where those 65 and over received 16 prescriptions per person by 1978-1979. The number of minor tranquillizing drugs dispensed under this plan continues to increase on a yearly basis, although at a slower rate than other drugs such as analgesics (pain killers). In Saskatchewan, the Joint Committee on Drug Utilization reported peak use of minor tranquillizers at age 75 for females and 65 for males.[36]

In Manitoba, 500 individuals over age 65 were studied who claimed their drugs under the province's Pharmacare program.[37] The benzodiazepines were the single most widely prescribed drugs with a high rate of steady use, 34 per cent in women and 22 per cent in men over 65 years of age. Converting to the whole population, not just those claiming under Pharmacare, the author concluded that over 20 per cent of Manitoba's females over age 65 were chronic users of benzodiazepines at the time of the study, 1975. Continuous use of two or more psychotropic drugs was found in 25 per cent of the women and 12 per cent of the men. In 1978 the author replicated his earlier study and found that the prescribing of psychotropic drugs had increased, especially for women.[38]

Concern regarding the potential health hazards of psychotropic drugs for the elderly is particularly relevant considering the findings of a recent English study.[39] Over 1000 repeat prescriptions of psychotropic drugs (given without the doctor seeing the patient) were examined from a

population of over 100 000 patients. It was found that the longer repeat prescribing had taken place, the older the patients were likely to be, and the less closely were they to be monitored by their general practitioners. Sixty-six per cent of the drugs monitored were benzodiazepines.

Since telephone prescribing is permitted in Canada and not in the United Kingdom, one might expect an equal or greater amount of repeat prescribing in Canada.

3. The Chronically Ill

A comprehensive review of the efficacy of benzodiazepines in somatic disorders, largely of a chronic nature, states that, generally, evidence of improved outcome due to anxiolytic effects is lacking.[40] The authors conclude that the role of these drugs is primarily adjunctive, i.e. facilitating patient management and improving the feeling of well-being without 'curing'. The conditions in which these drugs appear to have value adjunctively are acute myocardial infarction, migraine and gastrointestinal disorders. They appear to be contraindicated in respiratory conditions. The authors recommend careful assessment as to their value in adjunctive therapy as well as recommending only short-term benzodiazepine treatment.

A large study of elderly chronically ill patients in Ontario found that psychotropic drugs had been prescribed to about one-fourth of the patients, with benzodiazepines the most frequently prescribed class. Of those patients receiving at least one psychotropic drug prescription, 27 per cent had been prescribed two or three psychotropic drugs simultaneously.[41]

Other studies, largely outside of Canada, have examined the range of indications given for the use of these drugs in medical practice. A sample of such findings follows. As shown, most of the conditions listed are of a chronic nature, or potentially so.

In an American study, market research data was used for an analysis of indications for diazepam prescribing by a

random sample of physicians.[42] Non-psychiatric conditions accounted for 70 per cent of the diazepam users. Those included, in order of frequency, were musculoskeletal, circulatory, geriatric, medical-surgical aftercare, gastrointestinal, central nervous system disease, and genito-urinary problems. Diazepam had been prescribed in combination with other drugs in 64 per cent of the cases.

In a retrospective study of the indications for psychotropic drug treatment in general practice in Britain, it was found the 13 per cent of the patients had been prescribed psychotropic drugs during the year.[43] Both barbiturate hypno-sedatives and the minor tranquillizers Librium and Valium were commonly prescribed for disorders of menstruation and menopausal symptoms and for digestive system disorders such as duodenal ulcer, gastric ulcer, and colitis. Poorly defined symptoms which may have anxiety components, such as insomnia, headache, nervousness, dizziness, debility, backache, vague chest pains, precordial pains, palpitations, and tachycardia accounted for almost one-third of all patients prescribed psychotropics.

In contrast to the above results, a Finnish study of general practitioners found that 21 per cent of the diagnoses resulted in psychotropic drug treatment.[44] Thirty-nine per cent of the psychotropics were prescribed for somatic diseases while this was true for 85 per cent of the hidden psychotropics (combined drugs containing a benzodiazepine).

It would appear from the data cited that minor tranquillizers have been prescribed for a broader range of chronic conditions than have been identified as appropriate.[45a] Hemminki, in Finland, concluded that broadening the indications for use to many somatic diseases was an effective mechanism in increasing the use of psychotropic drugs.[45b] It should be noted that advertisements in medical journals frequently advise physicians to prescribe benzodiazepines to patients with a wide variety of chronic illnesses.

4. The Institutionalized

Far fewer studies have been reported of the institutionalized than of other high risk populations. Yet, recently published data indicate that this population, residing in nursing homes, retardation centres and prisons, may be prescribed the largest quantity of psychotropics.

The most comprehensive study of the institutionalized was conducted in American long-term care facilities (largely consisting of nursing homes). This study examined diagnostic and prescribing information for almost 300 000 patients with chronic diseases and disabling conditions. Tranquillizers (both major and minor) were prescribed to all those institutionalized patients with a diagnosis of alcoholism, to 52 per cent with a diagnosis of angina or myocardial infarct and to 50 per cent with a diagnosis of neurological disorder. Among those with other chronic conditions, 42 to 48 per cent were prescribed tranquillizers, suggesting that prescription of these drugs may frequently be unrelated to specific diagnosis but, as concluded by the authors, may be used for the purpose of institutional control.[46]

Two Canadian studies on this topic have been reported in the medical literature. The first examined drug use among residents in five retardation centres in Eastern Ontario.[47] It was found that 42 per cent of the residents were given psychotropic prescriptions. The majority of these were major tranquillizers while 21 per cent had used a variety of sedatives and hypnotics (largely benzodiazepines). In these institutions, epileptics and non-epileptics received the same proportion of psychotropic drugs. While the author does not distinguish major from minor tranquillizers in his discussion, he nonetheless concludes that "it is quite clear that at least half of the subjects on psychotropics were given those agents unnecessarily." A study of prisoners at Millhaven Penitentiary with a history of aggressive behaviour was carried out specifically to assess the effect of benzodiazepines on

aggression in this type of setting.[48] Using prisoners as their own controls, it was found that violent or aggressive incidents were most frequent when the men were using benzodiazepines.

Unfortunately, however, there is still a paucity of information on the use of benzodiazepines in Canadian institutional settings.

APPROPRIATE USES OF BENZODIAZEPINES

Use as Anti-Anxiety Agents and Hypnotics

Benzodiazepine drugs have a definite place in the armamentarium of the physician. The primary role of these drugs is as anti-anxiety agents in acute or chronic incapacitating disorders characterized by anxiety. Current practice defines these states as Generalized Anxiety Disorders and Panic Disorders.[49] Panic takes the form of unpredictable acute anxiety of sudden onset resulting in feelings of intense apprehension and frequently includes physical symptoms such as palpitations, breathlessness, chest pains, etc. Generalized Anxiety refers to continuing and steady severe anxiety lasting long after a stressful situation has occurred or without any precipitation stress.*

Numerous studies have demonstrated the superiority of benzodiazepines over placebo in reducing anxiety.[50] It is claimed, however, that some uncertainty still exists regarding the anti-anxiety properties of the benzodiazepines as separate from their well-established sedating effects.[51]

Severe insomnia is another condition for which these drugs are prescribed. Some benzodiazepines are promoted solely as hypnotics (e.g. flurazepam, triazolam), but a number of others, which first came on the market as anti-anxiety agents, are currently used in somewhat larger doses as sleeping medications (diazepam, oxazepam).

Use in Non-Psychiatric Conditions

Benzodiazepines have also been found to be useful in acute alcohol withdrawal. However, controlled conditions are recommended for the use of these drugs in withdrawal.[52] Other

*These states must be clearly distinguished from the type of anxiety commonly experienced by most individuals in response to situational stresses and which takes milder forms such as occasional sleeplessness, feelings of irritability and tension, and so forth.

uses include the treatment of some types of continuous seizures, and of a variety of neuromuscular disorders such as cerebral palsy, tetanus, and stiff-man syndrome.[53] Diazepam, in particular, is used extensively in pre-anaesthetic procedures, as an intravenous anaesthetic during minor surgery, and in a variety of diagnostic tests generally administered in hospitals.[54, 55]

One literature review of the efficacy of benzodiazepines in nonpsychiatric medical practice, particularly their effects on the cardiovascular and gastrointestinal systems, concludes with a plea for large clinical trials carried out over a prolonged time period. Because of currently conflicting evidence, such studies are judged necessary to answer the question whether the benzodiazepines "affect only anxiety and muscular tension or whether they also affect organ systems known to be linked in important pathophysiological ways to the nervous system."[56]

Psychiatric contraindications

While benzodiazepines have a clear role in diminishing acute anxiety they do not appear to be effective in treating severe psychiatric disorders such as schizophrenia. Nor have benzodiazepines been found superior to antidepressant drugs for depression,[57] although there is some evidence accumulating that they may be of value for depressive disorders in which anxiety is a major component.[58] As noted earlier, it would appear that these drugs are contraindicated in those disorders in which aggressive behaviour predominates,[59, 60] as they frequently release rage reactions and increase hostility. Such reactions have also been observed by clinicians in previously non-aggressive patients.

Duration of Use and Dosage

Given this wide spectrum of uses, the following discussion will focus on the most common uses, those associated with anxiety reduction and sleep disorders.

It is generally agreed that, lacking evidence that the anti-anxiety properties of these drugs exceed two to four weeks, and since anxiety is typically episodic, courses of one to two weeks are recommended.[61] Dependence on diazepam, the most extensively studied benzodiazepine, is estimated to occur anywhere from two weeks to four months after initial use, depending on dosage.[62]

Another reason for the recommended course of only one to two weeks, is the opportunity provided to assess the individual dose response. There is considerable evidence that dose requirements for patients vary greatly, to the extent that "... it is virtually impossible to predict a clinical response at a particular dose in a particular patient."[63]

Sensitivity to these drugs clearly increases with age (thus initial doses should be lower in older age groups than for younger people) as well as with some disorders, such as liver disease. Females appear to be less sensitive to diazepam than males, and smokers may require up to 50 per cent more compound than non-smokers for equivalent action.[64] Thus gender, age, smoking behaviour, liver functioning as well as recent use of other substances such as alcohol and other central nervous system drugs will profoundly affect the individual's response to benzodiazepines.

Appropriateness in Pregnancy, Pediatric Medicine, the Elderly

There are certain life stages during which benzodiazepines should be used only with caution and under very limited conditions. For example, there is now general agreement that these drugs, like many others, should rarely be used in the first trimester of pregnancy because of risks to the developing foetus.[65] Since pregnancy is typically not confirmed until four to six weeks after conception, use of these drugs is unwise for women of child-bearing age who are at risk of becoming pregnant. Because benzodiazepines cross the placental barrier and accumulate in the foetus when given in

a continued dosage regimen, there are problems associated with their use in the latter part of pregnancy and during labour. Newborn infants whose mothers have used these drugs for extended periods have shown a variety of symptoms such as respiratory distress and poor sucking. The abrupt withdrawal from the drugs at birth appears also to result in irritability, tremors, diarrhea and other disorders.[66]

Benzodiazepines accumulate in breast milk, causing possible sedation and feeding difficulties in the infant.[67] Thus, many women may prefer not to use these drugs during labour or immediately thereafter.

In childhood, a clear indication exists for use of benzodiazepines in the control of convulsions, in which intravenous as well as oral forms are used.[68] As with adults, these drugs are used in various anaesthetic procedures with children.

As mentioned earlier, sensitivity to these drugs increases with age, thus it is not surprising to find a higher incidence of side effects among the elderly. Excessive drowsiness and sedation are more than twice as common in the elderly after using diazepam than in a younger population.[69] It has been recommended that the drugs with a short half-life be used for this population. However, there is as yet no controlled research indicating their greater safety and efficacy over the older benzodiazepines. In addition, some recent clinical reports indicate there may be more severe problems on withdrawal from the short half-life benzodiazepines.

In view of their frequent use of multiple medications, their diminished capacity to metabolize and excrete drugs, and the current lack of clarity on the safest and most efficacious benzodiazepines to use in the elderly, careful monitoring of this population is particularly important.[70]

UNDESIRABLE PHYSIOLOGICAL AND PSYCHOSOCIAL CONSEQUENCES OF BENZODIAZEPINE USE

Any pharmacologically active substance which has positive effects is, unfortunately, likely to have negative effects on some individuals and under some conditions. Additionally, drugs which affect the central nervous system and alter mood are also likely to be used recreationally and inappropriately, regardless of their legal status. This section, then, will deal with some of the undesirable pharmacological and psychological consequences of use as well as problems associated with polydrug use, cross-addiction, overdose and self-poisoning.

Physical Effects

Tests to determine the safety and efficacy of prescription drugs are generally carried out on populations who are not typical of users of the substances. Clinical trials and laboratory studies are most commonly conducted on young, healthy, frequently male subjects under carefully controlled conditions. As shown earlier, the majority of benzodiazepine users are older, largely female and often using other medications for a variety of chronic conditions. Thus the applicability of the clinical test findings is seldom clear. However, combining clinical test results with actual cases reported in medical journals and data from benzodiazepine users permits a multifaceted view of the consequences of use of these drugs.

Most of the following discussion relates to continuous and long-term use of more than four months duration among people taking benzodiazepines at normal or above normal dose levels. Those problems which can arise after shorter use, such as motor impairment, will be identified as such.

1. Dependence and Withdrawal

Divisions of opinion exist regarding the dose and time necessary to produce dependence on benzodiazepines, although there is no longer any disagreement that dependence of a physical and/or psychological nature can occur. The major indication of dependence is the development of withdrawal symptoms, which have now been clearly established at therapeutic dose levels.[71-73]

There have been few systematic studies of problems associated with withdrawal following normal use,[74] and it is extremely difficult to establish any figures for the numbers of individuals currently dependent on these drugs. One such carefully controlled study of withdrawal symptoms in patients who had been on low doses of benzodiazepines for a mean of 3.6 years, found between 27 and 45 per cent evidencing clear withdrawal symptoms, varying by the measure of withdrawal used. Significantly, follow-up after three months found those who either refused to participate in the study or had dropped out during it had largely returned to benzodiazepine use while those who had successfully completed the withdrawal remained drug free. The authors concluded that, "The high incidence of withdrawal symptoms suggests that a substantial minority of patients taking benzodiazepines chronically are pharmacologically dependent."[75]

Many individuals will attempt withdrawal and quickly resume drug use because of symptoms such as lack of energy, sleeplessness, headache, trembling and nausea. These symptoms appear from 24 hours to 10 days following cessation of use, depending on the half-life of the benzodiazepine taken. In severe cases, where high doses are ingested, withdrawal can take forms similar to that found with alcohol or barbiturates, such as muscle twitches, seizures, weakness and tremors, confusion and psychosis.[76]

Many of the minor symptoms described above are common to drug effects as well as to the anxiety that may have

precipitated the drug use initially. Consequently, it has been frequently thought that all such reactions were the result of the predisposing condition. This cannot be so in all cases for a number of reasons: 1) neonates born to drug-dependent women have shown withdrawal symptoms; 2) acute anxiety is only one of many indications for use of these drugs and even that is generally episodic in nature; 3) in some patients withdrawal symptoms do not resemble those of anxiety, such as abrupt weight loss.[77]

Short-term therapy lasting less than four weeks with these drugs is not thought to produce dependence and withdrawal problems.[78]

2. Motor and Cognitive Impairment

A number of clinical and experimental studies have demonstrated psychomotor, learning and memory impairment following use of benzodiazepines.[79-81] Performance on a variety of commonly used tests, such as vigilance, memory, digit symbol substitution, and flicker fusion have all shown deficits in normal young adults using low doses of drugs. In a review of the literature which covered only controlled studies, it was found that learning and immediate memory are impaired by these drugs, that is, the deficit is particularly evident regarding the learning of new material. Memory for material learned prior to drug ingestion is not impaired.[82] The implications of this for continuous users of benzodiazepines may be considerable in terms of daily performance.

Numerous laboratory studies have demonstrated motor impairment following use of low doses of benzodiazepines[83, 84]. Studies under naturalistic conditions are few in number, since they are costly and difficult to administer. The first such large-scale study of driving impairment under 'natural' conditions, conducted in Britain, compared the prescribed medicines used by people in the three months prior to their injury or death driving a car, motorcycle or bicycle to those medicines used by a large number of matched controls.[85]

There was a highly significant association between use of minor tranquillizers and the risk of a serious road accident. The risk was also increased for antihistamines but not for a wide variety of noncentral nervous system drugs.*

Benzodiazepines as Hypnotics

A major American study has pointed out the lack of any standardized criteria for defining insomnia and unclear evidence of efficacy of any drugs for patients' complaints of insomnia.[86] Hypnotic drugs apparently reduce the time needed to fall asleep by only 10 to 20 minutes and lengthen total sleep time by 20 to 40 minutes thus raising a number of questions about the importance of hypnotics. Some researchers, however, suggest that the use of hypnotics provides other benefits when used for short periods.[87]

While initially focussing on the barbiturates, the report also examined the benzodiazepine hypnotics and found some potentially hazardous attributes of the longer acting benzodiazepines such as flurazepam (Dalmane) and diazepam which are not found with barbiturate hypnotics. These include: 1) an increased likelihood of adverse drug reactions with advancing age of the patient, and 2) a greater likelihood of adverse drug reactions in patients with diminished kidney function. The following hazards are common with both benzodiazepines and barbiturates: 1) there is a potential danger for overdose when combined with other depressant drugs; 2) following nighttime drug use, there are deficits demonstrated the following day on tests of visual-motor coordination; and 3) benzodiazepines and barbiturates are equally likely to lead to nightly reliance on drugs for sleep. (After a week of such use the impairment caused by long-acting benzodiazepines is greater than that resulting from nightly use of a barbiturate.)

*Unfortunately, alcohol comsumption and its possible role in these accidents could not be determined because of the design of this study.

Polydrug Use and Cross-Addiction

Polydrug use, or the concurrent use of more than one psychotropic substance, is a common pattern among benzodiazepine users. This multiple drug use reflects the widespread acceptance and easy availability of these drugs. Among the most commonly used drugs taken in combination are benzodiazepines with alcohol, other sedative-hypnotics, and narcotics. Studies of the extent and implications of polydrug use are relatively recent and not as comprehensive as is desirable. Concern with this phenomenon is with both deliberate and accidental overdose, the increased possibility of adverse drug interactions, and motor impairment resulting in traffic and other accidents.

It would appear that youthful experimenters and steady users tend to combine a variety of psychotropic drugs. A survey conducted for The National Commission on Marijuana and Drug Abuse in the United States found that young people who had consumed alcohol within the previous seven days were almost twice as likely to report ever using tranquillizers.[88]

Studies of adult drug users also report a high proportion of multiple users. A survey of Toronto adults reported that users of tranquillizers were over four times as likely to also be users of stimulants or barbiturates as were non-tranquillizer users.[89]

A Canada-wide survey of drug consumption found 27 per cent of those using tranquillizers simultaneously using sedative drugs, 10 per cent using antidepressants, five per cent using antispasmodics, five per cent antihistamines, and 15 per cent using analgesics. Conversely, half of the respondents who reported using a sedative in the previous three days also reported use of a tranquillizer during that period.[90]

The three studies described above do not indicate the source of the drugs consumed. However, a range of psychotropic drugs and other prescription drugs are often prescribed concurrently by one or more treating physicians. It is not

uncommon for an individual to be sent to a specialist and be given a prescription for a psychotropic drug while simultaneously using psychotropic medications prescribed by his general practitioner.

While surveys of large populations report considerable use of tranquillizers in combination with other licit drugs, studies of illicit drug users or abusers have shown an increased use of benzodiazepines among these populations. For example, CODAP, the Client Oriented Data Acquisition Process, presents data on clients admitted to treatment centres across the United States. Of those reporting tranquillizers as the primary drug of abuse in 1978, 73 per cent also reported abusing a second drug, usually alcohol. Those abusing alcohol and tranquillizers in combination tended to be older than those abusing other combinations of drugs.[91]

Benzodiazepines have rarely been systematically studied as an illicit drug. However, in a study of clients of the Philadelphia Veterans Administration Drug Dependence Centre, it was found that 29 per cent of the drug abuse patients had used street purchased diazepam in the month preceding the survey.[92] In 1975, patients on the methadone maintenance program at both the Narcotic Addiction Foundation of British Columbia and the Addiction Research Foundation of Ontario were assessed for benzodiazepine content in their urines.[93] The study found 47 per cent and 65 per cent positives, respectively, in Vancouver and Toronto. Because of the high incidence of use the Toronto investigators conducted 15 consecutive weekly screenings for benzodiazepines. They concluded that approximately 44 per cent of the methadone patients use benzodiazepines regularly or most of the time, receiving the drugs from physicians and other sources outside the Foundation.*

*The use of benzodiazepines as street drugs is frequently documented in newspaper accounts. For example, a recent seizure by Montreal police yielded 544 kilograms of diazepam powder illegally imported for purposes of trafficking. (*The Globe and Mail*, Toronto, May 22, 1981).

It is clear from these Canadian and American reports that benzodiazepines have become major street drugs. This should be expected of any popular and readily available mood-altering substance. As street drugs they are not likely to be used alone but rather in combination with either alcohol or hard drugs.

A hazard of polydrug use which has received relatively little study to date is the potential for increased motor impairment leading to traffic fatalities and industrial accidents. Major reasons for this are the high cost and methodological difficulties entailed in such research. The Traffic Injury Research Foundation of Canada analysed the presence of at least 90 psychotropic and other substances from drivers and pedestrians fatally injured in Ontario between 1978 and 1979. Of those found with diazepam in their bodies (three per cent of the victims), 44 per cent were also positive for alcohol; 38 per cent of the diazepam cases involved drugs other than alcohol.[94] However, there was no mention in the report of other benzodiazepines studied. This one Canadian study unfortunately analysed only traffic fatalities rather than including traffic injuries. One could hypothesize that heavy consumers of benzodiazepines, such as women and the elderly, are less likely 1) to be driving cars, and 2) to be driving at speeds likely to result in fatalities. In addition, it would have been desirable to obtain data on the presence of benzodiazepines in a matched control group of non-accident drivers.

In a study reviewing the data on drugs, alcohol and driving, its authors state that the high consumption of anti-anxiety drugs make them the most important group of prescription drugs in terms of traffic safety. They conclude that anti-anxiety drugs *per se* can increase traffic accident risk and the risk will be further increased when those drugs are combined with alcohol.[95]

Overdose and Poisoning

From Canadian and other sources it is clear that the drugs used in overdose reflect their availability.[96-98] Many overdoses are impulsive acts and therefore the indiviual tends to consume those substances readily at hand in the liquor or medicine cabinet. As sales of barbiturates have declined in recent years, overdose with these drugs has similarly declined and, conversely, benzodiazepine overdoses have risen with increased sales.

Because of the greater safety of benzodiazepines compared to the barbiturates, there are virtually no lethal overdoses reported for these drugs taken alone.[99] However, in combination with alcohol or other drugs benzodiazepines can be lethal.

The Drug Abuse Warning Network (DAWN) in the United States, covering emergency room overdose data between 1973 and 1976, found tranquillizer-involved cases accounted for the largest subgroup (43 per cent) of the emergency room suicide attempt cases. Valium was the second most frequently mentioned drug of abuse while alcohol in combination with other drugs was the most frequent.[100]

Studies conducted in emergency rooms of Canadian hospitals found from one-third to one-half of patients having used benzodiazepines.[101-103] Many of them had used these drugs in combination with alcohol.

The only national data source in Canada collecting overdose information is the Poison Control Program. Statistics are compiled annually from reports originating from hospitals designated as Poison Control Centres. Excluded are reports from the majority of hospitals in Canada, data from industry, physicians and paramedical personnel and from persons who attempt to handle this situation themselves. One group of researchers studying the data concluded that this federal system was probably aware of only 20 to 25 per cent of the total poisonings.[104] Bearing in mind these limitations, this data is useful in demonstrating trends over

time. For example, there was a 46 per cent increase in the reporting of Valium poisonings over the years 1970 to 1976. Over 13 per cent of all poisoning cases were accounted for by four benzodiazepines. Unlike ASA, iron preparations, Ex-Lax and acetaminophen, which were ingested primarily by children under four, the benzodiazepines studied were consumed largely by adults, suggesting fewer accidental occurrences and more deliberate overdoses.

An overdose study conducted in 21 Toronto hospitals found that patients using benzodiazepines with a long half-life, such as flurazepam, arrived at hospital drowsier and required inpatient care, in contrast to those who had ingested drugs with a shorter half-life.[105] In view of the increased sales of benzodiazepines with a shorter half-life (oxazepam, lorazepam), we may find equal numbers coming to emergency departments of hospitals but fewer admissions resulting from overdose with these drugs.

FACTORS AFFECTING PRESCRIBING AND CONSUMPTION

Physicians are the gatekeepers of the health care system. Their actions are, of course, determined in part by those whom they find at their gates. A climate of opinion has emerged both within the medical profession and the larger society whereby persons troubled in their family, work and personal lives for whatever reasons (e.g. problems of role definition, life goals, economic pressures, chronic physical illness), find themselves in the medical clinic or the physician's office. The introduction of universal health care has made access to these services available to virtually all segments of the population. Simultaneously, lack of knowledge of the existence of other social support services, the fees charged for these services, and the residual stigma still attached to them, continues to lead individuals to seek medical attention.

Numerous factors account for the change in the types of health problems presented to the physician over the last 35 years. Increased affluence has resulted in improved nutrition, sanitation, public health measures (especially preventive services for children), the development of anti-infective agents, and higher expectations of care on the part of consumers of health care services. Concurrently, the proportion of the population over age 65 has increased markedly.

With the reduction in the incidence of acute conditions such as pneumonia and measles, there has been a concomitant increase in the range of disorders presented to the physician. It is a minority of visits to physicians now which are the result of acute conditions; the majority of visits are taken up with conditions for which treatment of a medical and/or non-medical nature may be indicated. Among these are chronic conditions, problems associated with normal aging, and physical and emotional stresses arising from common problems of living, such as work pressures, family stresses, or social isolation.

The Biomedical Model of Illness

While the nature of the disorders which doctors are called upon to treat has changed, the basic education provided by the majority of Canadian medical schools continues to be based upon a philosophical model of illness which may not be appropriate to these changed conditions. Undergraduate medical education is largely taught by specialists who tend to perpetuate the 'disease model of illness' which in its essence sees the individual body as a machine to be repaired by chemical or mechanical intervention. While courses in public health and the behavioural sciences are offered in the medical curriculum and do not follow this biomedical model of illness, these courses represent a small percentage of total course offerings. As a result, medical education continues to be primarily oriented to the identification and treatment of disease through the use of technology. Surgical and pharmacological intervention are the primary modalities of care offered patients.[106]

Students entering general practice or certain specialties such as psychiatry may be exposed, by instructors as well as patients, to a broader concept of illness such as that developed by Engel, one which includes psychosocial factors in addition to mechanical malfunctioning.[107] This bio-psychosocial model takes into consideration psychosocial factors such as family disruption, stress at work, isolation of the aged. Hence the use of an additional treatment technique by physicians such as counselling for emotional problems may be utilized, and occasionally referral may be made to community counselling services. While such an approach recognizes the connection between mind and body, the location of the problem and hence its treatment is still presumed to lie within the individual.

Given this medical education, virtually all physicians today are trained as scientific problem-solvers rather than carers.[108] With its emphasis on treating disease, this training basically minimizes prevention and tends to encourage

physicians to focus on the malfunctioning organ or body system, rather than on the whole person within her/his social setting. For example, the definition of excessive consumption of alcohol as a disease has led to a greater emphasis on treatment and the search for cures for the end states of alcoholism (e.g. cirrhosis of the liver) than on the doctor's role as a preventive agent. The latter would involve learning the role of alcohol in the lives of patients, history-taking which would include information on the quantity consumed, factors influencing use, and so forth. More time is allotted in our medical schools to teaching treatment of the physical damage caused by alcohol than to teaching skills which will aid in the identification and early intervention with patients misusing alcohol.

This emphasis on treatment may also account for a great deal of the frustration felt by physicians in their contacts with the elderly and the chronically ill for whom high technology medicine holds few significant answers. There is at present a mismatch between the skills and training of physicians and the majority of problems seen in practice. With the growing elderly population this problem will become more severe.

The continuing emphasis on the biomedical model of disease tends to minimize expenditures on preventive services. This is evidenced by the high proportion of our total health budget spent on costly high technology equipment located in hospitals.[109]

Physician-Patient Relationships

The tendency to define all problems seen by the physician as having their source solely within the body or mind of the individual has profound implications for the prescribing of benzodiazepines. Social problems, often felt and expressed by the individual as emotional pain or distress, are commonly defined as psychological symptoms of a disease process.*

*For example, the elderly, chronically ill and women commonly experience poverty, poor housing, isolation and loneliness, inadequate work environments and opportunities, and so forth.

Once so defined, such a problem requires health care resources and active treatment by the physician. This treatment often takes the form of a benzodiazepine prescription. Such prescriptions can result in short-term positive consequences for the individual and the physician. In the case of some types of disordered sleep problems the use of a benzodiazepine for a few nights may provide a satisfactory solution. In the case of incapacitating anxiety, short-term benzodiazepine therapy may also provide enough immediate relief to permit counselling or other relevant interventions. It may also be the support, concern and time provided by the physician in the course of a visit which provides a measure of short-term relief. The patient may benefit through being relieved temporarily of difficult or burdensome obligations by being perceived as sick, thus experiencing diminished family responsibility, time off work, and increased sympathy. In such situations the doctor feels she/he has done something for his patient and thus relieves the doctor's frustration; simultaneously, by the giving of a pill the doctor's and the patient's belief that the locus of illness resides in the individual is reinforced.

While benefits from short-term drug use may clearly be seen, the underlying social problems causing the anxieties may be untouched by the continued use of medication and left ultimately unattended. The drug may, in fact, by masking the patient's feelings, diminish motivation to act. Continued use of benzodiazepines can also result in increased dependence both on the individual physician and frequently on institutions such as hospitals. In addition to the economic costs incurred by continuous use of physician services there may be a range of other costs to the patient. These could include a lessened sense of competence, lowered self-esteem, and a self-definition as 'sick', all of which may result in an inability to pursue resolution of his/her problems.

Physicians who continue to prescribe psychotropic drugs to patients presenting with such complaints are inadvertently transforming social problems into medical ones. In giving a drug the physician conveys the message to the patient that s/he has identified the problem, that the patient came to the proper place for treatment, and that it is the physician, not the patient or other segments of the community, who needs to take action or be involved. Through giving a drug, the physician defines the patient's discomfort as amenable to a medical solution, is satisfied that s/he has acted on the problem, and reduces the patient's anxiety by accepting responsibility for treatment.

Because of their training, physicians are likely to prefer to work with patients whose symptoms are definite and with whom, by applying their knowledge, they can facilitate healing. They frequently complain of the high proportion of patients appearing with 'vague' and 'trivial' complaints.[110] Because of the frustrations in this situation, the administration of a drug, even when based on the assumption of a partial placebo effect, may reduce the physician's feeling of helplessness.[111]

These frustrations arise, in part, from the fatalistic view held by the doctor that there is nothing s/he can do to alleviate or change an unpleasant life situation. Some of the great variation in prescribing of psychotropic drugs may be accounted for by the individual physician's philosophic view of his/her potential as a change agent, as well as by temperamental differences and variations in training. That is, some physicians, feeling there is little they can do to effect change, prefer not to discuss social stresses and may actively discourage such discussion on the part of patients. Such physicians may view insomnia as a legitimate basis for prescription of a sleeping medication, at the same time refusing to examine possible psychosocial bases of the sleep disorder.

On the other hand, physicians who recognize the relationship of social strains to the anxieties presented may either realize that chemical intervention is of little use in altering

poor life situations and consequently use these drugs minimally, or feel that the drugs may provide temporary relief and consider it more humane to provide them as a coping mechanism.

The variation in attitudes and beliefs regarding the prescription of these drugs has been strikingly demonstrated in a study conducted during 1977 by the Birmingham Research Unit of the Royal College of General Practitioners in Britain. The study found wide variation among family doctors in the rates at which psychotropic drugs were prescribed, to the extent of "a tenfold difference in the use of these drugs (40 per 1000 compared with 415 per 1000)."[112] These variations, perhaps more than anything else, illustrate the interplay of the many factors discussed above.

Organization of Medical Care

As with the biomedical model, the structure of health care services bears examination as it may affect prescribing patterns. Organizational features of our health care system and methods of financing it have been shown to influence many patterns of medical practice, such as rates of surgery and hospitalization. The following section will review the effects on prescribing of method of physician payment, size of practice, utilization review, and third-party payment for prescriptions.

It frequently has been assumed that method of physician payment would influence the rate of drug prescribing by permitting salaried physicians more time with patients than those working on a fee-for-service basis. Unfortunately, large-scale studies comparing the prescription rates of physicians paid by fee-for-service with those paid by salary or capitation are not available. One recent Canadian study has attempted an analysis of this issue through the use of simulated cases.[113] The study presented physicians with a simulated case of tension headache for which diazepam had been prescribed for the past year. Physicians in group practice working on a fee-for-service basis in the Montreal area were

compared to salaried physicians practising in health centres. The findings showed little difference in the proportion of physicians willing to prescribe diazepam. However, the salaried physicians imposed stricter time limits on their prescriptions, issued clearer warnings about drug use, and were more likely to suggest non-chemical therapies. The salaried physicians also spent a longer time with the patients which may be the major factor accounting for the differences found in their approach to prescribing.

The limited studies available in the literature suggest that physicians practising in group settings generally prescribe drugs more appropriately than physicians practising alone.[114] Although no Canadian studies exist on this topic, two American studies of patients receiving care from group practices found fewer drugs of all kinds prescribed, including tranquillizers, sedatives and hypnotics.[115, 116] While it is possible that practitioners in group practice are more skilled, or that differences in patient populations utilizing such practices explain some of the findings, it seems reasonable to conclude that practising in a group encourages discussion and continuing education on issues in medical care and thus may be an important factor associated with the quality of prescribing.

Group practices can permit the utilization of a wider variety of personnel, such as social workers, public health nurses, and nurse practitioners. The effect of introducing nurse practitioners as primary care workers in a family practice setting was assessed in a Canadian study and it was found that the use of nurse practitioners in contrast to traditional nursing staff clearly reduced the number of tranquillizing drugs prescribed.[117]

Group practice is, of course, not an automatic guarantee of high quality prescribing. Another factor affecting prescribing may be peer review. Periodic review of prescribing patterns has been proposed and partially adopted in a number of countries as a means of assessing and ultimately improving prescribing quality. Pressure for such reviews has

come from within government agencies as well as from the leadership of some medical groups such as the College of Family Physicians of Canada and the Royal College of General Practitioners in the United Kingdom. In the simplest form of such review, a physician may audit his/her own prescribing practices and compare this to what s/he deems appropriate, or to a pre-established norm. A potentially more valuable process is that in which a group of practitioners jointly review their prescribing practices and thus benefit collectively from a wider array of clinical experience. Finally, computerized prescription records of large populations may be used in utilization reviews.

One self-audit was conducted in a rural, northern Ontario practice.[118] The author aimed to review his own prescribing habits to learn for what types of patients he prescribed which drugs, to relate drug use to illness and to test a new method of reporting and measuring drug use. Through this analysis the author was able to compare his prescribing patterns and practices with that of many larger practices, thus deepening his understanding of his own behaviour. In his words, "A study of prescribing is a revealing exercise, which tells one more about the doctor than about his patients."

Peer reviews in group settings are considerably more frequent than self-audits. A study of the educational value of assessing prescribing of psychotropic drugs was conducted in an Irish group practice.[119] They found, for example, that a disproportionate number of patients were receiving psychotropic drugs on repeat prescriptions, a situation which they considered undesirable.

To assess drug utilization by large populations computerized prescription records are necessary. Such records may make it possible to study trends in prescribing, link different rates of prescribing to either physician or patient characteristics, identify particular high prescribers and consumers, examine prescription refill practices and finally, examine the relationship between drug taking and diagnosis.

Several Canadian provinces already have or are in the process of computerizing prescription records for that part of the population which is eligible for drug insurance benefits. Saskatchewan, which provides drug insurance for all provincial residents and has computerized all prescription records since 1977, has been able to study the utilization of tranquillizing drugs in the entire population. This monitoring has provided a means of educating all physicians. It has also permitted the identification of exceptionally high prescribing physicians and will provide ongoing information on shifts in prescribing patterns over time. Among other benefits, this continuous monitoring will facilitate the analysis of the impact of any drug education programs in the province.

Various professional associations of pharmacists have accepted a more active educational role for their members with regard to prescription review. This would include checking for excessive quantities, potential drug interactions, and adequacy of instructions to patients. All of the above would protect consumers and further assist physicians in appropriate prescribing. Saskatchewan, through the cooperation of the Colleges of Medicine and Pharmacy and the provincial pharmaceutical and medical associations, has developed a drug information service that has been in operation since 1974. The service is now available to all pharmacists and physicians in the province and is well utilized.[120]

There is some evidence to suggest that when prescriptions are insured, utilization of drugs increases.[121, 122] It has been demonstrated that surgical rates for discretionary procedures increased with the introduction of insurance plans.[123] Similarly, it may be that drug insurance would have its greatest impact on the utilization of medications for conditions which are not life threatening, such as those for which the benzodiazepines are prescribed. This was, in fact, demonstrated in a U.S. study examining prescriptions before and after the introduction of Medicaid, including medication insurance. Not only did drug utilization per patient almost double but, more important, the number of different drugs

used increased, as did the average quantity prescribed. Anti-anxiety agents comprised four per cent of the top 40 drugs in the pre-insurance period and almost 10 per cent after the introduction of insurance.[124]

A recent study in Britain appears to substantiate the above findings by demonstrating their converse. It shows that as the charges for individual prescriptions have increased, the total number of prescription sales have declined.[125]

While the data suggest that insurance for medication raises utilization rates and increased costs diminish rates, the question remains whether the increase in use following insurance introduction results from meeting previously unmet medication needs. Additionally, it is important to learn how much prescribing results in unnecessary or excessive use once cost constraints are removed. Lack of insurance may prevent some patients from acquiring essential drugs. However, the benzodiazepines cannot be considered life-saving or as a rule essential.

Drug Promotion and Advertising

Canadian prescribing patterns cannot be fully understood without an examination of the role of the pharmaceutical industry. The industry currently supports a wide assortment of promotional activities in addition to the drug advertisements appearing in medical journals and those mailed in bulk to all physicians.[126]

The effect of drug promotion and advertising on consumption of benzodiazepines are of concern to researchers and physicians in many parts of the world. For example, in his foreword to a publication of the Royal College of Psychiatrists, Professor Griffith Edwards recently wrote: "... I would make a strong plea for a line of research which is willing to examine the social and 'political' processes involved, rather than the focus being exclusively on the drug-using individual. We need to know very much more about the role of marketing and advertising in the burgeoning

sale of these substances both in urbanized and developing countries."[127]

There is little doubt that the industry in Canada, as elsewhere, expends considerable time and money informing physicians of its products.[128] At issue is the degree to which physicians do, and should, rely on the industry as their primary source of information on drugs. A second concern is the quality of the information disseminated. In recent years there has been a steady increase in the number of hours devoted to the teaching of pharmacology and clinical pharmacology in Canadian medical schools. Consequently, young Canadian physicians today can be expected to be more sophisticated in their approach to therapeutics. Unfortunately, however, there is little data available on sources of information used in the decision to prescribe. While change may well be occurring, the most recent studies in developed Western nations indicate that advertising and promotional materials are still central in the decision-making process.

The range of promotional activities includes direct mail advertising, expensive educational brochures and materials, and various gifts. In addition, the industry frequently sponsors major academic meetings, supports the publication of the proceedings of such meetings, and actually supports most of the drug research conducted.[129, 130]

In addition to these activities perhaps the most common sources of information for the practising physician are drug company representatives, popularly called 'detail men'. The function of these representatives is to visit individual physicians, hospital pharmacies and other prescribing institutions to inform them of new products provided by their company, new indications for use for older products, and to generally encourage acceptance of their company's products. Research conducted in the United States, the United Kingdom and the Scandinavian countries all concluded that practising physicians are reliant on detail men as a major source of information.[131-133]

It appears that the ratio of detail men to physicians varies markedly by country, with the Third World countries having the highest ratio and the more developed countries, particularly those in Europe, having the lowest ratio.[134] For example, there was a ratio of one representative to three physicians in Brazil and one to 32 in Norway between the years 1970 and 1974.

This same study examined the function of drug company representatives and concluded:

> "the companies regard detailing more as selling than as public relations. If detailing gives valuable pharmacological information, it is often only a by-product, used as a method of selling. The success of the representative is measured by the volume of sales, and not by improvements in the knowledge of physicians."[135]

In view of the significant role played by the pharmaceutical industry as a source of information, attention must turn to the quality of the information dispensed. A study of drug advertisements in both British and American journals found that the British advertisements seldom included information about drug interactions, contraindications, adverse reactions or mode of action. Advertisements in the American journals generally provided more information but still contained inadequate data for clinical judgment.[136] Advertisements in medical journals are frequently structured to appeal to physicians on an emotional basis through the illustrations, although the text and heading might stress factual information.[137]

Beyond a lack of information, advertisements directed to physicians have been criticized for their presentation of erroneous assumptions or false stereotypes. Psychotropic advertisements in particular have been found to encourage diagnosis 'at-a-glance'. They tend to promote extension of the definition of medical problems to encompass the stresses of daily living, and to further the belief that certain illnesses

must be 'coped with' through continuous drug consumption.[138] Several studies have demonstrated negative stereotyping of women and the elderly in drug advertisements, showing them as misfits who require drugs to endure, not change, their situations.[139-141]

SOCIAL MEANING OF BENZODIAZEPINE USE

The extensive consumption of benzodiazepines and their effect as mood-altering substances combine to raise important issues about the impact of these drugs on the individual and society. Numerous questions demand attention by the medical profession, social scientists and ultimately, policy makers. For example, given the sedating properties of these drugs and, with steady use, their potential for causing cognitive and learning impairment, how common is the masking of emotions? And, what effect does this masking have on dulling one's perceptions of reality? Do these pharmacological effects impair ability to deal with social strains and difficult life situations? Do they diminish motivation for change?

The paper has discussed how continuous drug use tends to create dependence and encourage the acceptance of chemicals as coping supports. Do they, over time, actively erode the individual's coping abilities?

A Canadian study which attempted to address some of these issues brought together benzodiazepine users to discuss their perceptions of the drugs' effects on their lives.[142] The population studied was largely female, in their middle years and somewhat more educated than the general population. They were almost uniformly long-term users though not at high dose levels.

Analysing the data thematically, continuing use was most understandable in terms of the problems of social roles expressed. Drug use was described as a means of maintaining themselves in roles which they found difficult or intolerable without the drug.

Women described their drug use as an aid in sustaining caring, nurturing relationships with their spouses and children. Many of the women described situations of extreme role strain. For some of the women, the strain arose from major problems or conflicts around the maternal role, conflicts often generated by a sickly or difficult infant or by a

lack of preparation for the isolation entailed in early child-rearing years. Some spoke of the drugs as a means of adapting to intolerable home situations, such as alcoholic behaviour in a spouse.

In many cases the strain was engendered by an inability to comply with traditional expectations (theirs as well as their husband's). These women commonly felt they lacked the 'right' to express their dissatisfactions and preferences. Some saw husbands as having other escape routes when marital obligations became burdensome, escapes which the women felt they lacked. While there were clear expressions of anger directed at their spouses, many of the women saw no alternative to continued occupancy of the traditional housewife role.

Male informants typically discussed their tranquillizer use in relation to job stresses and strains. They most commonly focussed on somatic symptoms brought on by work stresses or a change in jobs, and saw continued use of tranquillizers as a means of controlling these symptoms. A number accepted that little change in their job status was possible and therefore saw no means other than drugs to alleviate their symptoms.

The issues addressed by many informants were structural, and some, particularly those who had ceased or cut down their drug consumption, were able to describe structural as opposed to individual remedies to their problems. A number of the women found a return to work an aid in reshaping their lives, others gradually had altered marital relations, joined groups and acquired wider social supports. Some found more individualistic solutions through exercise or counselling.

To date, research has not addressed the impact of benzodiazepines on the family or on the interpersonal world of users. In the exploratory study described above, many people referred indirectly to changes in their family life which they attributed to these drugs. For example, one man described feelings of lethargy which affected the amount of time spent playing with his children. Others talked of dimi-

nished sex drive. Still others perceived positive effects, because they had less tendency to be irritable. During one group interview one person, who had stopped using benzodiazepines, commented on the impaired communication of members of the group who were using drugs at the time. The quality of family life and interpersonal relationships potentially affected by benzodiazepine use may be far-reaching given the proportion of our population consuming these drugs.

While use of benzodiazepines in family settings requires further study, some of the social meanings of their use in institutional settings have already been demonstrated. Little evidence exists of exact amounts dispensed through institutions, whether nursing homes, correctional institutions, or long-term care facilities. However, there appears to be little doubt that these drugs, along with other sedating drugs, are widely dispensed as a means of behavioural control. A major finding of a 15-year study of nursing homes across the United States stated that patients are tranquillized as a means of social control, to keep them quiet and therefore easier to look after. They also concluded, ironically, that it was precisely these same individuals who may be most favoured for rehabilitation.[143] The limitations of benzodiazepines used in this way were stated clearly by the Director of the National Institute on Aging: "... often drugs represent the only form of treatment given to older persons. An overall treatment plan that includes attention to diet, physical and social activities, psychotherapy and correction of living problems may be totally ignored."[144] With the increase in the proportion of elderly in Canada and the high rate of institutionalization of this age group, the use of sedating drugs may be used as a rough gauge of the value placed by society on the quality of life provided these members.

A major factor responsible for the acceptance of these drugs has been the pervasive mythology that there are instant solutions to problems of living and that the most effective

and rapid solutions are chemical in nature. Society has come to expect quick responses to any problem, whether it be the common cold, anxiety or grief. Through acceptance of this philosophy many people have come to view benzodiazepines as essentially a social and recreational drug, not unlike alcohol.

Because of the range of problems associated with steady use of benzodiazepines, it is apparent that these drugs cannot be viewed as substitutes for natural coping abilities. Thus it is important to examine alternatives to the use of chemicals as means of coping with the stresses of daily life. Efforts to provide support to other human beings, meaningful work and economic independence for all segments of the population, can begin the process of minimizing the need for these drugs. Simultaneously, the providers of benzodiazepines, the pharmaceutical industry, should omit references to problems of living from their advertisements and promotion as an indication for prescribing their products. Finally, the medical profession must become knowledgeable about the physical and psychosocial meanings of benzodiazepine use and then work together with their patients and the community to create acceptable and satisfying ways of coping.

SUMMARY AND CONCLUSION

This document has demonstrated that there are a variety of positive functions of benzodiazepine use, particularly in short-term use for control of acute anxiety, neuromuscular disorders and as an anti-convulsant. Efficacy as an anti-anxiety agent has not been demonstrated for longer than a few weeks and, because of the risk of dependency as well as with individual variation in dose response, continuous use should not exceed two weeks. Long-term use brings with it the increased access to the drug, which has been shown to be highly correlated with overdose and polydrug use. Also, the development of dependence and the impairment of cognitive and motor skills have been strongly suggested; this seems to be a function of the dose ingested as well as length of use. In addition, the higher consumption of benzodiazepines by particular high risk groups (e.g. the elderly, chronically ill and women) may lead to special problems for these segments of the population.

Underlying contemporary medical practice, the biomedical model defines the locus of all problems seen by the physician as residing within the individual. It follows, therefore, that all solutions must also be on an individual, i.e. biological, level. Coinciding historically with the development of this philosophical position was the growth and rapid development of new products by the pharmaceutical industry. The benzodiazepines were developed during a period in which acute illness was better controlled. Thus, increasing numbers of patients were presenting symptoms of chronic illness, normal problems of aging, social and interpersonal problems, and symptoms of anxiety and tensions related to all of the foregoing. The medical profession accepted these symptoms as legitimately within its domain for treatment.

The costs of continued use of benzodiazepines require careful consideration. The economic costs may be incurred by the individual or through third party payment. The concern with payment must extend beyond the price of pres-

criptions to the total cost to the health care system. Inappropriate prescribing may well keep individuals visiting physicians, the most expensive component of the system, for considerably longer than necessary. This does not, of course, include the physical and psychosocial costs incurred through toxic reactions, adverse reactions and overdose.

Although there are a paucity of studies relating benzodiazepine prescribing to aspects of medical organization, what data does exist would suggest that the chances of prescribing appropriately are greater in a group practice than a solo practice. It can be expected that prescribing would be optimized with peer reviews of drug utilization and improved communication through information on therapeutics provided by non-industrial sources.

In drawing conclusions regarding the issue of benzodiazepine use, there are no scientific absolutes or 'objectivity'. Having assessed the data, the authors have formulated a number of conclusions which, in their view, best reflect the relationship between the currently available data on these drugs and their assessment of the health and social care system in Canada.

Resulting from this examination of benzodiazepine use, we question whether many of the problems of living presented to physicians can be addressed in the health care system at all. Although recognizing the value of benzodiazepines in short-term care, their use poses serious questions regarding interference with individuals' abilities to alter their lives and thus cope with stresses without the aid of chemicals.

Given the large numbers of Canadians currently using benzodiazepines, the possibilities of impaired decision-making, decreased learning skills, released aggression and impaired ability to empathize have a significance extending beyond the lives of these individuals to the community at large.

These consequences of use are common to a variety of mood-altering substances such as alcohol, marijuana, and other illicit drugs as well as benzodiazepines. With the exception of alcohol, a larger proportion of the adult population probably uses benzodiazepines on any given day than uses any illicit drug. For this reason, attention to social and legal facets of use is required.

A major concern are those populations at highest risk of receiving these drugs. The populations discussed share common problems and disadvantages in Canada today. These include poor economic conditions, inadequate housing, low social status, frequently inadequate support structures such as day care and community services to maintain the elderly and the chronically ill outside of institutions.

If, as suggested, benzodiazepines are used to dull social pain, then alternative solutions must be found which meet the needs of both individuals and society. The authors recognize that alternatives are being attempted in select communities. However, by articulating the problems associated with benzodiazepine use, it is hoped that this document will contribute to the further development of new concepts of prevention and new models of care.

APPENDIX A
BENZODIAZEPINES SOLD IN CANADA, 1981

Generic Name	Canadian Trade Names (Manufacturer)	Date of Introduction
chlordiazepoxide hydrochloride: methaminodiazepoxide hydrochloride	Corax (ICN) C Tran (Beecham) Librium (Roche) Medilium (Medic) Novopoxide (Novopharm) Relaxil (Maney) Relium (Riva) Solium (Horner) Trilium (Trianon) also generically by: (Drug Trading); (Duchesnay); (Interlab); (Pro Doc); (Quebec Pharmaceutiques); (Sands)	1960
clonazepam	Rivotril (Roche)	1976
clorazepate dipotassium	Tranxene (Roche)	1973
diazepam	D Tran (Beecham) E Pam (ICN) Meval (Medic) Neo Calme (Neo) Novodipam (Novopharm) Rival (Riva) Stress-Pam (Sabex) Valium (Roche) Vivol (Horner) also generically by: (Drug Trading); (Pro Doc); (Quebec Pharmaceutiques); (Sands)	1962
flurazepam hydrochloride	Dalmane (Roche) Novoflupam (Novopharm)	1970
flurazepam monohydrochloride	Somnol (Horner)	1981
lorazepam	Ativan (Wyeth)	1977
nitrazepam	Mogadon (Roche)	1981

oxazepam	Apo Oxazepam (Apotex) Ox-Pam (ICN) Serax (Wyeth) also generically by: (Drug Trading)	1965
temazepam	Restoril (Anca)	1981
triazolam	Halcion (Upjohn)	1980

Sources:

Canadian Pharmaceutical Association. *Compendium of Pharmaceuticals and Specialties*, Sixteenth Edition, 1981, Health and Welfare Canada.
Canadian Drug Identification Code, Seventh Edition, 1980.

APPENDIX B
GLOSSARY OF MEDICAL AND DRUG-RELATED TERMS

acetaminophen — (paracetamol), a mild pain reliever, which also reduces fever, e.g. Tylenol

adjunctive — adding to or accompanying in a subordinate category

anaesthetic — an agent that produces local or general loss of feeling or sensation

analgesic — a drug which relieves pain

angina — a disease marked by spasmodic attacks of intense suffocative pain

anticholinergic — a drug that blocks the effects of acetylcholine, a chemical produced naturally by the body and responsible for certain nervous system activities; these drugs inhibit the secretion of acid in the stomach, slow the passage of food through the digestive system, inhibit the production of saliva, sweat, and bronchial secretions, and increase the heart rate

antihistamine — a drug used to lessen or counteract the effects of histamine, a chemical produced by the body in response to various allergy-causing agents

antispasmodic — a drug used to quiet the spasms of voluntary and/or involuntary muscles, usually of the gastrointestinal tract

anxiolytic — a drug used to relieve anxiety

armamentarium — the entire equipment of a practitioner, such as medicines, instruments, books, etc.

ASA — acetylsalicylic acid, a mild pain reliever, e.g. Aspirin

barbiturates — derivatives of the barbituric acid, which produce central nervous system (CNS) depression, ranging from sedation to coma

clinical pharmacology — that aspect of pharmacology concerned with the study of drugs used in the prevention, diagnosis, and treatment of human disease

colitis — inflammation of the colon

contraindication — an indication, symptom, or condition that makes inadvisable a particular treatment or procedure

digit symbol substitution test — one of the 11 sub-tests of the Wechsler Adult Intelligence Scale. Performance on the test is taken as a measure of the efficiency of the processes of immediate rote recall, visual-motor integration, and visual imagery.

efficacy — the power to produce an effect

epidemiology — science dealing with the incidence, distribution, and control of disease in a population

flicker fusion tests — particular tests used to assess the general state of arousal of the central nervous system

generic — nonproprietary; denoting a drug name not protected by a trademark; sometimes called 'public name'

hypnotic — an agent that dulls the senses or induces sleep

illicit — illegal

indication — a symptom or particular circumstance that indicates the advisability or necessity of a therapy

metabolism of drugs — all the processes involved in the utilization of drugs entering the body

metabolite — any substance produced by metabolism

methadone — a narcotic drug administered usually in the form of its bitter crystalline hydrochloride for the relief of pain, and usually used in the treatment of narcotic dependence

modality — any of several methods utilized in therapy

myocardial infarction — necrosis or death of a portion of the heart muscle, from interruption or curtailment of its blood supply

narcotic — a drug that in moderate doses relieves pain and induces profound sleep. It has a high potential for addiction leading to abuse

pathophysiology — the physiology of abnormal states, specifically the functional changes that accompany a particular syndrome or disease

pharmacology — study of the history, source, biochemical and physiological effects, mechanisms of action, absorption, distribution, biotransformation and excretion, therapeutic and other uses of drugs

precordial — situated or occurring in front of the heart; involving the precordium

psychosomatic — resulting from the influence of emotional stress or conflict on a predisposed somatic area, organ, or bodily system

psychotropic — as used in this document, refers only to those drugs sold on prescription which have the ability to modify mood, but does not include analgesics

sedative — an agent which allays activity and excitement, and has a calming effect. Sedatives/hypnotics are frequently referred to as one category in clinical practice since their effects can range from sedation to hypnosis depending on the dose given

serum — the fluid portion of the blood obtained after coagulation, distinguished from the circulating plasma in blood

somatic — pertaining to the body

tachycardia — excessively rapid heart rate

therapeutic — pertaining to the treatment of disease

trade name — a name used by a company to identify its product as a unique entity

tranquillizer — an agent which has a calming effect without impairing consciousness. Tranquillizers are usually divided into two groups, major and minor, although considerable confusion surrounds the use of these terms. Major tranquillizers are of use in treating serious disorders such as mania and schizophrenia and are often called anti-psychotic drugs. They also produce a neuroleptic state and are sometimes called neuroleptics. Minor tranquillizers were thus named to distinguish them from major tranquillizers, because they are not effective in serious psychological disorders. They are sometimes called anti-anxiety drugs or anxiolytics be-

cause they are used to treat patients suffering from anxiety. Alternatively, minor tranquillizers and sedatives are sometimes grouped together under the heading anxiolytic sedatives

vigilance tests — performance tasks designed to measure the level or state of readiness of the nervous system, and its ability to detect and respond to certain specified small changes occurring at random time intervals in the environment

REFERENCES

1. Sellers, E. M., "Clinical Pharmacology and Therapeutics of Benzodiazepines", *Canadian Medical Association Journal*, 1978, *118* (1533).

2. *ibid*.

3. United States Department of Health, Education, and Welfare, "Prescribed and Nonprescribed Medicines: Type and Use of Medicines, United States, July 1964 — June 1965", *Vital and Health Statistics*, 1967, Series 10, Number 39, p. 2.

4. Fejer, D. and Smart, R., "The Use of Psychoactive Drugs by Adults", *Canadian Psychiatric Association Journal*, 1973, *18* (4): 313-320.

5. Smart, R. G. and Goodstadt, M. S., "Alcohol and Drug Use among Ontario Adults: Report of a Household Survey, 1976". Toronto: Addiction Research Foundation, Substudy No. 798, 1976.

6. Provisional Results of Gallup Survey, 1977. Commissioned by Non-Medical Use of Drugs Directorate, Department of National Health and Welfare, Ottawa.

7. Schuster, C. R., Bergman, J. and Hartel, C. R., *Assessing the Impact on Public Health, Individual Deficit, and Organ System Damage Associated with Psychoactive Substance Use*. Rockville, Maryland: National Institute on Drug Abuse, International Activities Program, August 1980, p. 76.

8a. Saskatchewan Joint Committee on Drug Utilization, Report No. 3, 3475 Albert St., Regina, Canada, October 1979.

8b. Personal communication from Mr. George Peters, Saskatchewan Prescription Drug Plan, Saskatchewan Department of Health, Regina, Saskatchewan.

9. Ontario Ministry of Health, Annual Ontario Prescription Survey, "Distribution of Psychotropic Prescriptions in Ontario, 1970-1978".

10. Schuster *et al.*, 1980, *op. cit.*

11. Anderson, R. M., "The Use of Repeatedly Prescribed Medicines", (Prescribing in General Practice 3), *Journal of the Royal College of General Practitioners*, 1980, *30*: 609-613.

12. Saskatchewan Joint Committee on Drug Utilization, 1979, *op. cit.*

13. *ibid.*

14. Chaiton, A., Spitzer, W. O., Roberts, R. S., and Delmore, T., "Patterns of Medical Drug Use — A Community Focus", *Canadian Medical Association Journal*, 1976, *114* (1): 33-37.

15. Guse, L., Morier, G., and Ludwig, J., "Winnipeg Survey of Prescription (Mood Altering) Drug Use among Women". Technical Report, NMUDD, Manitoba Alcoholism Foundation, October 1976.

16. Archer, C. and Benner, M. "Women's Use of Psychotropic Medication: A Community Survey", *Canadian Family Physician*, 1980, 26: 867-871.

17. Cooperstock, R., "Psychotropic Drug Use among Women", *Canadian Medical Association Journal*, 1976, *115:* 760-763.

18. Gallup Survey, 1977, *op. cit.*

19. Bass, M. and Paul, D., "The Influence of Sex on Tranquillizer Prescribing". Paper presented at the North American Primary Care Research Group Meeting, March 1977, Williamsburg, Virginia.

20. Cooperstock, 1976, *op. cit.*

21. *ibid.*

22. Pflanz, M., Basler, H., and Schwoon, D., "Use of Tranquillizing Drugs by a Middle-Aged Population in a Western German City", *Journal of Health and Social Behavior*, 1977, *18* (2): 194-205.

23. Chambers, C. D., Inciardi, J. A., and Siegal, H. A., *Chemical Coping: The Extent of Non-Addicting Drug Use in the United States*. New York: Spectrum Publications, 1974.

24. Guse *et al.*, 1976, *op. cit.*

25. *ibid.*

26. *ibid.*

27. Archer and Benner, 1980, *op. cit.*

28. Greenblatt, D. J., Shader, R. I., and Koch-Weser, J., "Psychotropic Drug Use in the Boston Area", *Archives of General Psychiatry*, 1975, *32* (4): 518-521.

29. Frey, D. D., Hetherington, R. W., and Glassman, D., "The Use of Prescription Drugs — Treatment of First Time Psychiatric Admissions to University Hospital, Saskatchewan", *Social Science and Medicine, 1978, 12* (3A): 169-174.

30. Bass and Paul, 1977, *op. cit.*

31. Horwitz, A., "The Pathways into Psychiatric Treatment: Some Differences between Men and Women", *Journal of Health and Social Behavior*, 1977, *18* (2): 169-178.

32. *ibid.*

33. Phillips, D. L., and Segal, B. E., "Sexual Status and Psychiatric Symptoms", *American Sociological Review*, 1969, *34* (1) : 58-72.

34. Hurwitz, N., "Predisposing Factors in Adverse Reactions to Drugs", *British Medical Journal*, 1969, *1* (5643) : 536-539.

35. Ontario Council of Health, *Health Care for the Aged*, Toronto, 1978.

36. Saskatchewan Joint Committee on Drug Utilization, 1979, *op. cit.*

37. Mitenko, P. A., "Drug Use in the Elderly", *Drug Merchandizing*, June 1978 59: 37-42.

38. Mitenko, P. A., Hildahl, V. K., Large, G. W., Aoki, F. Y., and Sitar, D. S., "Drug Use in the Elderly (Manitoba — 1978)", *Clinical Research*, 1980, *28*: 665A.

39. Dennis, P. J., "Monitoring of Psychotropic Drug Prescribing in General Practice", *British Medical Journal*, 1979, 2 (6198): 1115-1116.

40. Krogh, C., McLean, W. M., and La Pierre, Y. D., "Minor Tranquillizers in Somatic Disorders", *Canadian Medical Association Journal*, May 6, 1978, *118* (9): 1097-1108.

41. Achong, M. R., Bayne, J. R. D., Gerson, L. W., and Golshani, S., "Prescribing of Psychoactive Drugs for Chronically Ill Elderly Patients", *Canadian Medical Association Journal*, June 24, 1978, *118*: 1503-1508.

42. Blackwell, B., "Psychotropic Drugs in Use Today: The role of Diazepam in Medical Practice", *Journal of the American Medical Association*, 1973, *225* (13): 1637-1641.

43. Parish, P. A., "The Prescribing of Psychotropic Drugs in General Practice", *Journal of the Royal College of General Practitioners*, Supplement No. 4, 1971, *21* (92): 1-77.

44. Hemminki, E., "General Practitioners' Indications for Psychotropic Drugs", *Scandinavian Journal of Social Medicine*, 1974, 2: 79-85.

45a. Krogh *et al.*, 1978, *op. cit.*

45b. Hemminki, 1974, *op. cit.*

46. Subcommittee on Long-Term Care of the Special Committee on Aging, United States Senate. *Nursing Home Care in the United States: Failure in Public Policy*. Supporting Paper No. 2: "Drugs in Nursing Homes: Misuse, High Costs, and Kick-backs". January 1975, 95th Congress, 1st Session, Washington, D.C.: U. S. Government Printing House.

47. Tu, J.-D., "A Survey of Psychotropic Medication in Mental Retardation Facilities", *Journal of Clinical Psychiatry*, 1979, *40*: 125-128.

48. Workman, D. G., and Cunningham, D. G., "Effect of Psychotropic Drugs on Aggression in a Prison Setting", *Canadian Family Physician*, 1975, *21* (11): 63-66.

49. *Diagnostic and Statistical Manual of Mental Disorders*. Third Edition, Washington, D.C.: American Psychiatric Association, 1980.

50. Greenblatt, D. J., and Shader, R. I., "Benzodiazepines", *The New England Journal of Medicine*, 1974, *291* (19, 23): 1011-1015, 1239-1243.

51. Bellantuono, C., Reggi, V., Tognoni, G., and Garattini, S., "Benzodiazepines: Clinical Pharmacology and Therapeutic Use", *Drugs*, 1980, *19* (3): 195-219.

52. Sellers, E. M. and Kalant, H., "Alcohol Intoxication and Withdrawal", *New England Journal of Medicine*, 1976, *294*: 757-762.

53. Sellers, 1978, *op. cit.*

54. Greenblatt and Shader, 1974, *op. cit.*

55. Bellantuono *et al.*, 1980, *op. cit.*

56. Lasagna, L., "The Role of Benzodiazepines in Nonpsychiatric Medical Practice", *American Journal of Psychiatry*, 1977, *134* (6): 656-658.

57. Bellantuono *et al.*, 1980, *op. cit.*

58. Schuster, 1980, *op. cit.*

59. Workman and Cunningham, 1975, *op. cit.*

60. Brown, C. R., "The Effect of Benzodiazepines in Prison Populations", *Journal of Clinical Psychiatry*, 1978, *39* (3): 219-222.

61. Schuster *et al.*, 1980, *op. cit.*

62. United States Senate, *Use and Abuse of Benzodiazepines*, Transcript of a hearing before the Subcommittee on Health and Scientific Research of the Committee on Labor and Human Resources. Washington, D.C.: U. S. Government Printing Office, 1980.

63. Sellers, 1978, *op. cit.*

64. Greenblatt, D. J. and Shader, R. I., "Effects of Age and Other Drugs on Benzodiazepine Kinetics." Paper presented at symposium, New Perspectives in Benzodiazepine Therapy, Heidelberg University, Heidelberg, Germany, 1980.

65. Sellers, 1978, *op. cit.*

66. Bellantuono *et al.*, 1980, *op. cit.*

67. Allen, M. D. and Greenblatt, D. J., "Hypnotics and Sedatives", in Dukes, M. N. G. (ed), *Side Effects of Drugs Annual 3*, Amsterdam: Excerpta Medica, 1979.

68. Graham, P., "Management in Child Psychiatry: Recent Trends", *British Journal of Psychiatry*, 1976, *129*: 97-108.

69. Boston Collaborative Drug Surveillance Program, "Clinical Depression of the Central Nervous System Due to Diazepam and Chlordiazepoxide in Relation to Cigarette Smoking and Age", *New England Journal of Medicine*, 1973, *288*: 277-280.

70 Committee on the Review of Medicines, "Systematic Review of the Benzodiazepines", *British Medical Journal*, 1980, *280* (6218): 910-912.

71. Preskorn, S. H. and Denner, L. J., "Benzodiazepines and Withdrawal Psychosis", *Journal of the American Medical Association*, 1977, *237* (1): 36-38.

72. Covi, L., Lipman, R. S., Pattison, J. H., Derogatis, L. R., and Uhlenluth, E. H., "Length of Treatment with Anxiolytic Sedatives and Response to Their Sudden Withdrawal", *Acta Psychiatrica Scandinavia*, 1973, *49*: 51-64.

73. Pevnick, J. S., Jasinski, D. R., and Haertzen, C. A., "Abrupt Withdrawal from Therapeutically Administered Diazepam", *Archives of General Psychiatry*, 1978, *35*: 995-998.

74. Greenblatt, D. J. and Shader, R. I., "Dependence, Tolerance, and Addiction to Benzodiazepines: Clinical and Pharmacokinetic Considerations", *Drug Metabolism Reviews*, 1978, *8* (1): 13-28.

75. Tyrer, P., Rutherford, D., and Huggett, T., "Benzodiazepine Withdrawal Symptoms and Propranolol," *The Lancet*, March 7, 1981, 520-522.

76. "Benzodiazepine Withdrawal", *The Lancet*, January 27, 1979, *1* (8109): 196.

77. *ibid*.

78. Sellers, 1978, *op. cit*.

79. Götestam, K. G. and Andersson, B. E., "Subjective Effects and Vigilance after Diazepam and Oxazepam in Normal Subjects", *Acta Psychiatrica Scandinavica*, 1978, *S274*: 117-121.

80. Gottschalk, L. A., "Effects of Certain Benzodiazepine Derivatives on Disorganization of Thought as Manifested in Speech", *Current Therapeutic Research*, 1977, *21* (2): 192-206.

81. Wittenborn, J. R., "Effects of Benzodiazepines on Psychomotor Performance", *British Journal of Clinical Pharmacology*, Supplement 1, 1979, 7: 61-67.

82. *ibid*.

83. Kleinknecht, R. A. and Donaldson, D., "A Review of the Effects of Diazepam on Cognitive and Psychomotor Performance", *The Journal of Nervous and Mental Disease*, 1975, *161* (6): 399-411.

84. Liljequist, R. and Mattila, M. J., "Acute Effects of Temazepam and Nitrazepam on Psychomotor Skills and Memory", *Acta Pharmacologica Toxicologica*, 1979, *44* (5): 364-369.

85. Skegg, D. C. G., Richards, S. M., and Doll, R., "Minor Tranquillizers and Road Accidents", *British Medical Journal*, 1979, *1* (6168): 917-919.

86. Solomon, F., White, C. C., Parron, D. L., and Mendelson, W. B., "Sleeping Pills, Insomnia and Medical Practice", *New England Journal of Medicine*, 1979, *300* (14): 803-808.

87. Roth, T., Zorick, F., Sicklesteel, J., and Stepanski, E., "Effects of Benzodiazepines on Sleep and Wakefulness", *British Journal of Clinical Pharmacology*, 1981, *11* (1S): 31S-35S.

88. Abelson, H., Cohen, R., Schrayer, D., and Rappeport, M., *Drug Experience, Attitudes, and Related Behavior among Adolescents and Adults. Part 1. Main Findings*. Princeton: Response Analysis Corporation, 1973.

89. Fejer and Smart, 1973, *op. cit*.

90. Gallup, 1977, *op. cit.*

91. CODAP: Data from the Client Oriented Data Acquisition Process (CODAP). *Annual Summary Report, 1978*, National Institute on Drug Abuse, Statistical Series E, No. 11, 1978.

92. Woody, G. E., O'Brien, C. P., and Greenstein, R., "Misuse and Abuse of Diazepam: An Increasingly Common Medical Problem", *The International Journal of the Addictions*, 1975, *10* (5): 843-848.

93. Kapur, B. M., Everson, A., Segal, R., and LeBlanc, A. E., "Benzodiazepine Analysis as a Monitoring Tool". Paper presented at the Ninth International Congress of Clinical Chemistry, Toronto, July 14-18, 1975.

94. Cimbura, G., Warren, R. A., Bennett, R. C., Lucas, D. M., and Simpson, H. M., *Drugs Detected in Fatally Injured Drivers and Pedestrians in the Province of Ontario*, Ottawa: Traffic Injury Research Foundation of Canada, March 1980.

95. Seppala, T., Linnoila, M., and Mattila, M. J., "Drugs, Alcohol and Driving", *Drugs*, 1979, *17*: 389-408.

96. Ruedy, J., "Acute Drug Poisoning in the Adult", *Canadian Medical Association Journal*, 1973, *109* (9): 603-608.

97. Johnson, F. G., Frankel, B. G., Ferrence, R. G., Jarvis, G. K., and Whitehead, P. C., "Self-Injury in London, Canada: A Prospective Study", *Canadian Journal of Public Health*, 1975, *66* (4): 307-316.

98. Proudfoot, A. T. and Park, J., "Changing Pattern of Drugs Used for Self-Poisoning", *British Medical Journal*, 1978, *1*: 90-93.

99. Finkle, B. S., McCloskey, K. L., and Goodman, L. S., "Diazepam and Drug-Associated Deaths", *Journal of the American Medical Association*, 1979, *242*: 429-434.

100. DAWN: *Project Dawn, Annual Report — 1978*, Drug Enforcement Agency and National Institute on Drug Abuse, Washington, D.C., 1980.

101. Ruedy, 1973, *op. cit.*

102. Rangno, R. E., "Epidemiology and Therapy of Suicidal Drug Intoxication", in Sellers, E. M. (ed), *Clinical Pharmacology of Psychoactive Drugs*. Toronto: Addiction Research Foundation, 1975, pp. 43-54.

103. Busto, U., Kaplan, H. L., and Sellers, E. M., "Benzodiazepine Associated Emergencies in Toronto", *American Journal of Psychiatry*, 1980, *137*: 224-227.

104. Sims, M., Purdy, M., and Devenyi, P., "Drug Overdoses in a Canadian City", *American Journal of Public Health*, 1973, *63* (3): 215-226.

105. Busto *et al.*, 1980, *op. cit.*

106. Smith, A., "Doctor in Need of a Cure". *Times Higher Education Supplement*, 3.4.81.

107. Engel, G. L. "The Need for a New Medical Model: A challenge for Biomedicine", *Science*, April 8, 1977, *196* (4286): 129-136.

108. Kennedy, I., *Unmasking Medicine*, Reith Lecture, 1980, London: British Broadcasting Corporation.

109. Castonguay, I. G., *Expenditures of the Health Care System in Ontario 1970/71 to 1977/78*, Ontario Ministry of Treasury and Economics, Central Statistical Services, Toronto, May 1981.

110. Mechanic, D., "Correlates of Frustration among British General Practitioners", *Journal of Health and Social Behavior*, 1970, *11*: 87-104.

111. Cartwright, A. *Patients and Their Doctors*. London: Routledge and Kegan Paul, 1967.

112. Birmingham Research Unit of the Royal College of General Practitioners, "Practice Activity Analysis. 4. Psychotropic Drugs". *Journal of the Royal College of General Practitioners*, *28* (187): 122-124.

113. Renaud, M., Beauchemin, J., Lalonde, C., Poirier, H., and Berthiaume, S., "Practice Settings and Prescribing Profiles: The Simulation of Tension Headaches to General Practitioners Working in Different Practice Settings in the Montreal Area", *American Journal of Public Health*, 1980, *70* (10): 1068-1073.

114. Stolley, P. D., Becker, M. H., Lasagna, L., McEvilla, J. D., and Sloane, L. M., "The Relationship between Physician Characteristics and Prescribing Appropriateness", *Medical Care*, 1972, *10* (1): 17-18.

115. Baron, S. H., and Fisher, S., "Use of Psychotropic Drug Prescriptions in a Prepaid Group Practice Plan", *Public Health Reports*, 1962, *77*: 871-881.

116. Rabin, D. L. Personal Communication, 1977.

117. Chaiton *et al.*, 1976, *op. cit.*

118. Dixon, A. S., "Drug Use in Family Practice: A Personal Study", *Canadian Family Physician*, 1978, *24*: 345-353.

119. Reilly, P. M. and Patten, M. P., "An Audit of Prescribing by Peer Review". Prescribing in General Practice 1, *Journal of the Royal College of General Practitioners*, 1978, *28* (194): 525-530.

120. Blackburn, J. L., Laxdal, O. E., and Dempsey, M. J., "Saskatchewan Dial-Access Drug Information Service", *Canadian Medical Association Journal*, 1976, *115*: 869-871.

121. Greenlick, M. R. and Darsky, B. J., "A Comparison of General Drug Utilization in a Metropolitan Community with Utilization under a Drug Prepayment Plan", *American Journal of Public Health*, 1968, *58*: 2121-2135.

122. Stolley *et al.*, 1972, *op. cit.*

123. Vayda, E., "A Comparison of Surgical Rates in Canada and in England and Wales", *The New England Journal of Medicine*, 1973, *289* (23): 1224-1229.

124. Smith, M. C. and Garner, D. D., "Effects of a Medicaid Program on Prescription Drug Availability and Acquisition", *Medical Care*, 1974, *12* (7): 571-581.

125. Office of Health Economics, *Effects of Prescription Charges*, London, December 1980.

126. Pharmaceutical Manufacturers Association of Canada, *The Pharmaceutical Industry and Ontario*, Ottawa, 1978, pp. 34-35.

127. Murray, R., Ghodse, H., Harris, C., Williams, D., Williams, P. (eds), *The Misuse of Psychotropic Drugs*, London: Gaskell (The Royal College of Psychiatrists), Special Publication 1, 1981.

128. Brooke, P., "Promotional Parameters: A Preliminary Examination of Promotional Expenditures", *Journal of Drug Issues*, 1976, *6* (1): 21-27.

129. Sellers, E. M., "Clinical Pharmacology in Canada", *Clinical Pharmacology and Therapeutics*, 1974, *16* (3, Part 2): 543-624.

130. Reekie, W. D., *The Economics of the Pharmaceutical Industry*, London: The Macmillan Press Ltd., 1975.

131. Walker, H. D., *Market Power and Price Levels in the Ethical Drug Industry*, Bloomington: Indiana University Press, 1971.

132. Linn, L. S., and Davis, M. S., "Physicians' Orientation toward the Legitimacy of Drug Use and Their Preferred Source of New Drug Information", *Social Science and Medicine*, 1972, *6*: 199.

133. Hemminki, E., "Review of Literature on the Factors Affecting Drug Prescribing", *Social Science and Medicine*, 1975, *9*: 111-115.

134. Hemminki, E. and Pesonen, T., "The Function of Drug Company Representatives", *Scandinavian Journal of Social Medicine*, 1977, *5*: 105-114.

135. *ibid*.

136. Morgan, H. A., Jeffers, T. A., Petrie, J. C., and Walker, W., "Drug Advertising in Medical Journals", *British Journal of Clinical Pharmacology*, 1976, *3*: 1057-1060.

137. Smith, M. C., "Appeals Used in Advertisements for Psychotropic Drugs: An exploratory Study", *American Journal of Public Health*, 1977, *67* (2): 171-173.

138. Stimson, G. V., "The Message of Psychotropic Drug Ads", *Journal of Communication*, 1975, *25* (3): 153-160.

139. King, E., "Sex Bias in Psychoactive Drug Advertisements", *Psychiatry*, 1980, *43*: 129-137.

140. Smith, M. C., "Portrayal of the Elderly in Prescription Drug Advertising", *The Gerontologist*, 1976, *16* (4): 329-334.

141. Mosher, E. H., "Portrayal of Women in Drug Advertising: A Medical Betrayal", *Journal of Drug Issues*, 1976, *6* (1): 72-78.

142. Cooperstock, R., and Lennard, H., "Some Social Meanings of Tranquillizer Use", *Sociology of Health and Illness*, 1979, *1* (3): 331-347.

143. Subcommittee on Long-Term Care of the Special Committee on Aging, United States Senate, 1975, *op. cit*.

144. Butler, R. N., "Public Interest Report No. 19 — The Overuse of Tranquillizers in Older Patients", *International Journal of Aging and Human Development*, 1976, *7* (2): 185-187.